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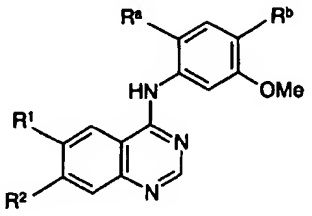
(54) Title: QUINAZOLINE DERIVATIVES



(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula I, wherein each of R^1, R^2, R^a and R^b have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification

includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn, Fyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, is frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer

(Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

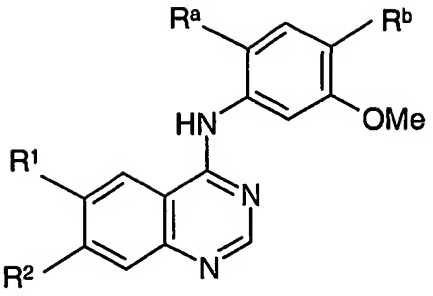
We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24 , 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

Generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory ativity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor tyrosine kinase.

According to one aspect of the invention there is provided a quinazoline derivative of the Formula I



I

wherein :-

$\mathbf{R^a}$ is chloro, bromo or iodo;

$\mathbf{R^b}$ is chloro, bromo or iodo;

$\mathbf{R^1}$ is hydrogen or (1-6C)alkoxy and $\mathbf{R^2}$ is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or $\mathbf{R^2}$ is a group of the formula :

$$-X^2\text{-}R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl, di-[(1-6C)alkyl]amino-(3-6C)alkyl, (2-6C)alkanoylamino-(3-6C)alkyl or (1-6C)alkoxycarbonylamino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^2 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, CH=CH and C≡C wherein R^7 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^7)$, R^7 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^8)$, CO, $CH(OR^8)$, $CON(R^8)$, $N(R^8)CO$, $SO_2N(R^8)$, $N(R^8)SO_2$, $C(R^8)_2O$, $C(R^8)_2S$ and $N(R^8)C(R^8)_2$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo or thioxo substituents;

or wherein $\mathbf{R^2}$ is hydrogen or (1-6C)alkoxy and $\mathbf{R^1}$ is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or $\mathbf{R^1}$ is a group of the formula :

$$-X^2\text{-}R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl, di-[(1-6C)alkyl]amino-(3-6C)alkyl, (2-6C)alkanoylamino-(3-6C)alkyl or (1-6C)alkoxycarbonylamino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, CH=CH and C≡C wherein R^7 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^7)$, R^7 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4\text{-}Q^2$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^8)$, CO, $CH(OR^8)$, $CON(R^8)$, $N(R^8)CO$, $SO_2N(R^8)$, $N(R^8)SO_2$, $C(R^8)_2O$, $C(R^8)_2S$ and $N(R^8)C(R^8)_2$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are

specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for Q^2 or Q^3 when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, conveniently phenyl.

A suitable value for Q^2 when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for Q^2 when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^3) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^3) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms

selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, conveniently pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl, homopiperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, a heteroaryloxy-(1-6C)alkyl, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl group is present.

Suitable values for any of the 'R' groups (R^1 to R^{11}), or for various groups within an R^1 or R^2 substituent, or for various groups within Q^1, Q^2 or Q^3 include :-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl and propionyl;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;
for (2-6C)alkanoylamino:	acetamido and propionamido;
for N-(1-6C)alkyl-(2-6C)alkanoylamino:	N-methylacetamido and N-methylpropionamido;
for N-(1-6C)alkylsulphamoyl:	N-methylsulphamoyl and N-ethylsulphamoyl;
for N,N-di-[(1-6C)alkyl]sulphamoyl:	N,N-dimethylsulphamoyl;
for (1-6C)alkanesulphonylamino:	methanesulphonylamino and ethanesulphonylamino;
for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino:	N-methylmethanesulphonylamino and N-methylethanesulphonylamino;
for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
for (1-6C)alkylamino-(1-6C)alkyl:	methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
for halogeno-(1-6C)alkyl:	chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
for (1-6C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
for (2-6C)alkanoylamino-(1-6C)alkyl:	acetamidomethyl, propionamidomethyl and 2-acetamidoethyl;

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl;

for amino-(3-6C)alkyl: 3-aminopropyl;

for (1-6C)alkylamino-(3-6C)alkyl: 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(3-6C)alkyl: 3-dimethylaminopropyl, 3-(N-ethyl-N-methylamino)propyl and 3-(N-isopropyl-N-methylamino)propyl;

for hydroxy-(3-6C)alkyl: 3-hydroxypropyl;

for (1-6C)alkoxy-(3-6C)alkyl: 3-methoxypropyl;

for (2-6C)alkanoylamino-(3-6C)alkyl: 3-acetamidopropyl; and

for (1-6C)alkoxycarbonylamino-(3-6C)alkyl: 3-methoxycarbonylaminopropyl.

When, as defined hereinbefore, an R^1 or R^2 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 or R^2 substituent bears a group of the formula -X^4-Q^2 and, for example, X^4 is a $C(R^8)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^8)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^2 group.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 or R^2 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^7)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 or R^2 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 or R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable

R^1 or R^2 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, R^a and R^b has any of the meanings defined hereinbefore or in paragraphs (a) to (l) hereinafter :-

(a) R^1 is hydrogen or methoxy and R^2 is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or R^2 is a group of the formula :

$$-X^2-R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl or di-[(1-6C)alkyl]amino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^2 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (2-6C)alkanoyloxy, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, $N(R^8)$, $CON(R^8)$, $N(R^8)CO$ and $C(R^8)_2O$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

(b) R^2 is hydrogen or methoxy and R^1 is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or R^1 is a group of the formula :

$$-X^2-R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl or di-[(1-6C)alkyl]amino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and (2-6C)alkanoyloxy, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, $N(R^8)$, $CON(R^8)$, $N(R^8)CO$ and $C(R^8)_2O$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(c) R^1 is hydrogen or methoxy and R^2 is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 2-(2-, 3- or 4-pyridyloxy)ethyl, 3-(2-, 3- or 4-pyridyloxy)propyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-azetidin-1-ylethyl, 3-azetidin-1-ylpropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperidin-3-ylethyl, 2-piperidin-4-ylethyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

or R^2 is a group of the formula :

$$-X^2-R^5$$

wherein X^2 is selected from O and NH and R^5 is 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-aminopropyl, 3-methylaminopropyl, 3-ethylaminopropyl, 3-isopropylaminopropyl, 3-dimethylaminopropyl, 3-diethylaminopropyl, 3-(N-cyclobutyl-N-methylamino)propyl, 3-(N-ethyl-N-methylamino)propyl, 3-(N-ethyl-N-isopropylamino)propyl or 3-(N-isopropyl-N-methylamino)propyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^2 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methyl, ethyl, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino, dimethylamino, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, isopentanoyloxy, cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^2 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, methyl, ethyl, cyclopropyl, allyl, methoxy, acetyl and tert-butoxycarbonyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and NH and R^9 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl,

methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O and NH and Q^3 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

(d) R^2 is hydrogen or methoxy and R^1 is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 2-(2-, 3- or 4-pyridyloxy)ethyl, 3-(2-, 3- or 4-pyridyloxy)propyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-azetidin-1-ylethyl, 3-azetidin-1-ylpropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperidin-3-ylethyl, 2-piperidin-4-ylethyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

or R^1 is a group of the formula :

$$-X^2-R^5$$

wherein X^2 is selected from O and NH and R^5 is 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-aminopropyl, 3-methylaminopropyl, 3-ethylaminopropyl,

3-isopropylaminopropyl, 3-dimethylaminopropyl, 3-diethylaminopropyl, 3-(N-cyclobutyl-N-methylamino)propyl, 3-(N-ethyl-N-methylamino)propyl, 3-(N-ethyl-N-isopropylamino)propyl or 3-(N-isopropyl-N-methylamino)propyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methyl, ethyl, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino, dimethylamino, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, isopentanoyloxy, cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^2 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, methyl, ethyl, cyclopropyl, allyl, methoxy, acetyl and tert-butoxycarbonyl, or optionally bears 1 substituent selected from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and NH and R^9 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

$-X^6-Q^3$

wherein X^6 is a direct bond or is selected from O and NH and Q^3 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(e) R^1 is hydrogen or methoxy and R^2 is 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrid-2-yloxyethoxy, 2-pyrid-3-yloxyethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-3-yloxypropoxy, 3-pyrid-4-yloxypropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-azetidin-1-ylethoxy, 3-azetidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

or R^2 is a group selected from 3-hydroxypropoxy, 3-methoxypropoxy, 3-ethoxypropoxy, 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(N-cyclobutyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-isopropylamino)propoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^2 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methyl, ethyl, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino, dimethylamino and acetoxy,

and wherein any pyridyl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl and methoxy, and a piperidin-3-yl, piperidin-4-yl or piperazin-1-yl group within a R^2 substituent is optionally N-substituted with cyclopropyl, allyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

(f) R^2 is hydrogen or methoxy and R^1 is 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrid-2-yloxyethoxy, 2-pyrid-3-yloxyethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-3-yloxypropoxy, 3-pyrid-4-yloxypropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-azetidin-1-ylethoxy, 3-azetidin-1-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy,

pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

or R^1 is a group selected from 3-hydroxypropoxy, 3-methoxypropoxy, 3-ethoxypropoxy, 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(N-cyclobutyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-isopropylamino)propoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methyl, ethyl, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino, dimethylamino and acetoxy,

and wherein any pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl and methoxy, and a piperidin-3-yl, piperidin-4-yl or piperazin-1-yl group within a R^1 substituent is optionally N-substituted with cyclopropyl, allyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl,

2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(g) R^1 is methoxy and R^2 is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

or R^2 is a group selected from 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any pyridyl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

(h) R^2 is methoxy and R^1 is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

or R^1 is a group selected from 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(i) R^a is chloro or bromo;

(j) R^a is chloro;

(k) R^b is chloro or bromo; and

(l) R^b is chloro.

A particular compound of the invention is a quinazoline derivative of the Formula I wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

or R^2 is a group selected from 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any pyridyl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 3-azetidin-1-yl-2-hydroxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy, 2-hydroxy-3-piperazin-1-ylpropoxy, 3-homopiperazin-1-ylpropoxy or 2-hydroxy-3-homopiperazin-1-ylpropoxy,

or R^2 is a group selected from 3-methylaminopropoxy, 2-hydroxy-3-methylaminopropoxy, 3-ethylaminopropoxy, 3-ethylamino-2-hydroxypropoxy, 3-isopropylaminopropoxy, 2-hydroxy-3-isopropylaminopropoxy, 3-dimethylaminopropoxy,

3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(N-ethyl-N-isopropylamino)propoxy, 3-(N-ethyl-N-isopropylamino)-2-hydroxypropoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)-2-hydroxypropoxy, 3-(N-isopropyl-N-methylamino)propoxy or 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, cyclopropyl, allyl, methoxy and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy or 2-hydroxy-3-piperazin-1-ylpropoxy,

or R^2 is a group selected from 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(N-ethyl-N-isopropylamino)propoxy, 3-(N-ethyl-N-isopropylamino)-2-hydroxypropoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)-2-hydroxypropoxy, 3-(N-isopropyl-N-methylamino)propoxy or 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, cyclopropyl, allyl, methoxy and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

R^a is chloro; and

R^b is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

R^1 is methoxy and R^2 is 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy or 2-hydroxy-3-piperazin-1-ylpropoxy,

or R^2 is 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears a hydroxy group on each said CH_2 or CH_3 group,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

R^a is chloro; and

R^b is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

A particular compound of the invention is, for example, a quinazoline derivative of the Formula I selected from :-

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

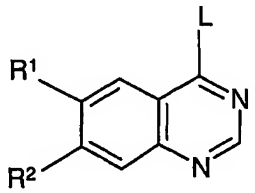
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline and

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

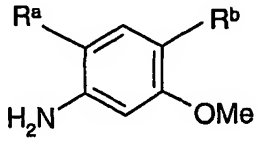
A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1, R^2 and R^3 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) The reaction, conveniently in the presence of a suitable acid or base, of a quinazoline of the Formula II



II

wherein L is a displaceable group and R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an aniline of the Formula III



III

wherein R^a and R^b have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal hydride, for example sodium hydride.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 80°C.

Typically, the quinazoline of the Formula II may be reacted with an aniline of the Formula III in the presence of a protic solvent such as isopropanol, conveniently in the presence of a suitable acid, for example hydrogen chloride gas in diethyl ether, or hydrochloric acid, and at a temperature in the range, for example, 0 to 150°C, preferably at or near the reflux temperature of the reaction solvent.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl,

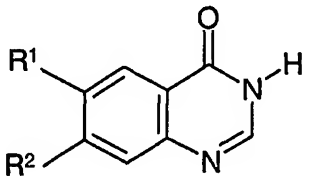
2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures. For example, a 3,4-dihydroquinazolin-4-one of Formula IV



IV

wherein R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

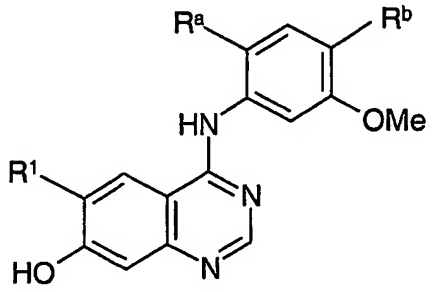
(b) For the production of those compounds of the Formula I wherein R^2 is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of an alcohol of the Formula

$$Q^1\text{-OH}$$

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a quinazoline of the Formula V

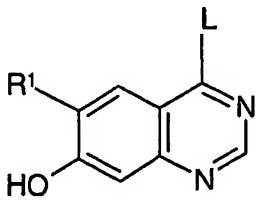


V

wherein R^1, R^a and R^b have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The quinazoline of the Formula V may be obtained by conventional procedures. For example, a quinazoline of the Formula VI



VI

wherein L is a displaceable group as defined hereinbefore and R^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted

with an aniline of the Formula III as defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

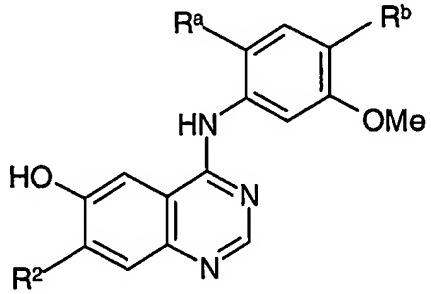
(c) For the production of those compounds of the Formula I wherein R^1 is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent as defined hereinbefore, of an alcohol of the Formula

$$Q^1\text{-OH}$$

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a quinazoline of the Formula VII



VII

wherein R^2, R^a and R^b have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The quinazoline of the Formula VII may be obtained by conventional procedures analogous to those described hereinbefore for the preparation of the quinazoline of the Formula V.

(d) For the production of those compounds of the Formula I wherein R^1 or R^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-piperidinopropoxy, 2-hydroxy-3-methylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy or 3-[N-(3-dimethylaminopropyl)-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein R^1 or R^2 contains an epoxy-substituted (1-6C)alkoxy

group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(e) For the production of those compounds of the Formula I wherein R^1 or R^2 contains an amino-acyloxy-disubstituted (1-6C)alkoxy group (such as a 2-isobutyryloxy-3-pyrrolidin-1-ylpropoxy group), the acylation of a compound of the Formula I wherein R^1 or R^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group.

The acylation reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature. For example, the acylation reaction may be carried out by the reaction of a compound of the Formula I wherein R^1 or R^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group with an appropriate carboxylic acid, conveniently in the presence of a suitable dehydrating agent as defined hereinbefore.

(f) For the production of those compounds of the Formula I wherein an R^1 or R^2 group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R^1 or R^2 group contains a protected hydroxy group.

Suitable protecting groups for a hydroxy group are, for example, any of the protecting groups disclosed hereinbefore. Suitable methods for the cleavage of such hydroxy protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkanoyl group such as an acetyl group which may be cleaved under conventional reaction conditions such as under base-catalysed conditions, for example in the presence of ammonia.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

A substrate solution [100µl of a 20µg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50µl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100µl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100µl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for

1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5×10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM). The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturating solution (FixDenat solution, Boehringer

Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC_{50} value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. ATCC CCL185) were suspended at a concentration of 2×10^7 cells/ml in the medium and maintained at a temperature of 37°C.

A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-containing droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO_2 : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC_{50} was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5 x 10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (b):- IC_{50} in the range, for example, 0.01 - 20 μM;

Test (c):- activity in the range, for example, 0.01-25 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for

example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to

progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. Particularly, the quinazoline derivatives of the present invention are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

The anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide,

nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products

employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1 **4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline dihydrochloride salt**

A mixture of 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (0.1 g), 2,4-dichloro-5-methoxyaniline (0.066 g), a 6M solution of hydrogen chloride in isopropanol (0.1 ml) and isopropanol (4 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature and the precipitate was isolated, washed in turn with isopropanol and diethyl ether and dried under vacuum. There was thus obtained the title compound (0.106 g); NMR Spectrum: ($DMSOd_6$) 1.6-17.5 (m, 2H), 2.02 (d, 2H), 2.15 (br s, 1H), 2.75 (d, 3H), 3.0 (m, 2H), 3.15-3.3 (m, 2H), 3.9 (s, 3H), 4.05 (s, 3H), 4.1 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H), 10.35 (br s, 1H); Mass Spectrum: $M+H^+$ 477 and 479.

The 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H), 1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: ($CDCl_3$) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: ($CDCl_3$) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

A portion (40 g) of the material so obtained was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6 g) and potassium carbonate (28 g) in DMF (200 ml) and the resultant mixture was stirred and heated to 95°C for 2.5 hours. The mixture was cooled to ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was collected by filtration, washed with petroleum ether and dried under vacuum. There was thus obtained ethyl 4-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-3-methoxybenzoate (35 g), m.p. 81-83°C; NMR Spectrum: ($CDCl_3$) 1.2-1.35 (m, 2H), 1.4 (t, 3H), 1.48 (s, 9H), 1.8-1.9 (d, 2H), 2.0-2.15 (m, 2H), 2.75 (t, 2H), 3.9 (d, 2H), 3.95 (s, 3H), 4.05-4.25 (br s, 2H), 4.35 (q, 2H), 6.85 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H).

The material so obtained was dissolved in formic acid (35 ml), formaldehyde (12M, 37% in water, 35 ml) was added and the mixture was stirred and heated to 95°C for 3 hours. The resultant mixture was evaporated. The residue was dissolved in methylene chloride and hydrogen chloride (3M solution in diethyl ether; 40 ml) was added. The mixture was diluted with diethyl ether and the mixture was triturated until a solid was formed. The solid was collected, washed with diethyl ether and dried under vacuum overnight at 50°C. There was thus obtained ethyl 3-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (30.6 g);

NMR Spectrum: ($DMSOd_6$) 1.29 (t, 3H), 1.5-1.7 (m, 2H), 1.95 (d, 2H), 2.0-2.15 (br s, 1H), 2.72 (s, 3H), 2.9-3.1 (m, 2H), 3.35-3.5 (br s, 2H), 3.85 (s, 3H), 3.9-4.05 (br s, 2H), 4.3 (q, 2H), 7.1 (d, 1H), 7.48 (s, 1H), 7.6 (d, 1H).

The material so obtained was dissolved in methylene chloride (75 ml) and the solution was cooled in an ice-bath to 0-5°C. Trifluoroacetic acid (37.5 ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming nitric acid (24M; 7.42 ml) in methylene chloride (15 ml). The resultant solution was allowed to warm to ambient temperature and was stirred for 2 hours. Volatile materials were evaporated. The residue was dissolved in methylene chloride (50 ml) and the solution was cooled in an ice-bath to 0-5°C. Diethyl ether was added and the resultant precipitate was collected and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500 ml) and hydrogen chloride (3M solution in diethyl ether; 30 ml) was added followed by diethyl ether (500 ml). The resultant solid was collected and dried under vacuum at 50°C. There was thus obtained ethyl 5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)-2-nitrobenzoate (28.4 g); NMR Spectrum: ($DMSOd_6$) 1.3 (t, 3H), 1.45-1.65 (m, 2H), 1.75-2.1 (m, 3H), 2.75 (s, 3H), 2.9-3.05 (m, 2H), 3.4-3.5 (d, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 4.3 (q, 2H), 7.32 (s, 1H), 7.66 (s, 1H).

A mixture of a portion (3.89 g) of the material so obtained, 10% platinum-on-activated carbon (50% wet, 0.389 g) and methanol (80 ml) was stirred under 1.8 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30 ml) and basified to pH10 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic layer was separated. The aqueous layer was further extracted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic extracts were combined, washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of petroleum ether (b.p. 60-80°C) and diethyl ether. The solid so obtained was isolated, washed with petroleum ether and dried under vacuum at 60°C. There was thus obtained ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (2.58 g), m.p. 111-112°C; NMR Spectrum: ($CDCl_3$) 1.35 (t, 3H), 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (t, 2H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.85 (d, 2H), 4.3 (q, 2H), 5.55 (br s, 2H), 6.13 (s, 1H), 7.33 (s, 1H).

A mixture of ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (16.1 g), formamidine acetic acid salt (5.2 g) and 2-methoxyethanol (160 ml) was stirred and heated at 115°C for 2 hours. Further formamidine acetic acid salt (10.4 g) was added in

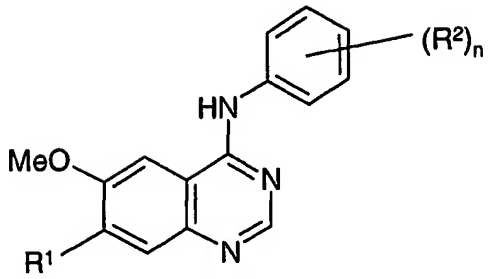
portions every 30 minutes during 4 hours and heating was continued for 30 minutes after the last addition. The resultant mixture was evaporated. The solid residue was stirred under a mixture of methylene chloride (50ml) and ethanol (100ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The resultant suspension was cooled to 5°C. The solid so obtained was collected, washed with cold ethanol and with diethyl ether and dried under vacuum at 60°C. There was thus obtained 6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7 g); NMR Spectrum: ($DMSOd_6$) 1.25-1.4 (m, 2H), 1.75 (d, 2H), 1.9 (t, 1H), 1.9 (s, 3H), 2.16 (s, 2H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.97 (s, 1H).

A mixture of a portion (2.8 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.28 ml) was heated to reflux for 1 hour. The mixture was evaporated and the precipitate was triturated under diethyl ether. The resultant solid was isolated and washed with diethyl ether. The solid was then dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (2.9 g); NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H), 1.75-1.9 (m, 4H), 2.0 (t, 1H), 2.25 (s, 3H), 2.85 (d, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

Example 2

Using an analogous procedure to that described in Example 1, the appropriate 4-chloroquinazoline was reacted with the appropriate aniline to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I



Compound No. & Note	R^1	$(R^2)_n$
[1]	piperidin-4-ylmethoxy	2,4-dichloro-5-methoxy
[2]	2-(N-methylpiperidin-4-yl)ethoxy	2,4-dichloro-5-methoxy
[3]	2-piperidin-4-ylethoxy	2,4-dichloro-5-methoxy
[4]	3-piperazin-1-ylpropoxy	2,4-dichloro-5-methoxy
[5]	3-morpholinopropoxy	2,4-dichloro-5-methoxy
[6]	2-acetoxy-3-morpholinopropoxy	2,4-dichloro-5-methoxy
[7]	2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy	2,4-dichloro-5-methoxy
[8]	2-acetoxy-3-piperidinopropoxy	2,4-dichloro-5-methoxy
[9]	2-acetoxy-3-pyrrolidin-1-ylpropoxy	2,4-dichloro-5-methoxy
[10]	2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy	2,4-dichloro-5-methoxy

Notes

[1] 7-(N-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 1.5-1.7 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (m, 1H), 2.9-3.05 (m, 2H), 3.4-3.5 (m, 2H), 3.9 (s, 3H), 4.06 (s, 3H), 4.11 (d, 2H), 7.43 (s, 1H), 7.48 (s, 1H), 7.83 (s, 1H), 8.34 (s, 1H), 8.80 (s, 1H), 8.7-8.8 (m, 1H), 9.0-9.1 (m, 1H); Mass Spectrum: $M\text{-}H^-$ 461 and 463.

The 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml).

The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: ($DMSOd_6$) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); NMR Spectrum: ($DMSOd_6$) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Example 1 that is concerned with the preparation of starting materials, 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine to give 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g) and a saturated methanolic ammonia solution (100ml) was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was isolated, washed with a 49:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (3.3 g); NMR Spectrum: ($DMSOd_6$) 1.12-1.3 (m,

2H), 1.42 (s, 9H), 1.8 (d, 2H), 2.02 (m, 1H), 2.7-2.9 (m, 2H), 3.9 (s, 3H), 4.02 (d, 4H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H).

A mixture of a portion (0.2 g) of the material so obtained, carbon tetrachloride (0.15 ml), triphenylphosphine (0.25 g) and 1,2-dichloroethane (10 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline (0.07 g); NMR Spectrum: ($DMSOd_6$) 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.08 (m, 1H), 2.7-2.9 (m, 2H), 4.02 (m, 5H), 4.12 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 408.

[2] The reaction product so obtained was mixed with methylene chloride (5 ml) and a saturated methanolic ammonia solution (0.5 ml) was added. The mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in diethyl ether and a 3M solution of hydrogen chloride in diethyl ether (0.5 ml) was added. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the dihydrochloride salt of the required compound which gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.4-1.55 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (d, 2H), 2.75 (s, 3H), 2.95 (m, 2H), 3.42 (d, 2H), 3.85 (s, 3H), 3.98 (s, 3H), 4.25 (m, 2H), 7.32 (s, 1H), 7.38 (s, 1H), 7.7 (s, 1H), 8.12 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 491 and 493.

The 4-chloro-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline used as a starting material is described in International Patent Application WO 00/47212 (example 241 thereof).

[3] 7-[2-(N-tert-Butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (d, 2H), 2.95 (m, 2H), 3.32 (d, 2H), 3.91 (s, 3H), 4.03 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.45 (s, 1H), 7.8 (s, 1H), 8.16 (s, 1H), 8.87 (s, 1H); Mass Spectrum: $M-H^-$ 475 and 477.

The 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g), N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine (2.84 g), potassium carbonate (1.8 g) and DMF (20 ml) was stirred and heated to 95°C for 2.5 hours. The resultant mixture was cooled to ambient temperature and poured onto a mixture of ice and water. The mixture was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 2H), 1.15 (s, 9H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.92 (s, 3H), 3.9-4.0 (m, 2H), 4.2 (m, 2H), 5.92 (s, 2H), 7.2 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Note [1] immediately above that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g) was treated with a saturated methanolic ammonia solution to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (1.3 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.3-3.5 (m, 2H), 3.9 (s, 3H), 3.9-4.0 (m, 2H), 4.18 (m, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 404.

Using an analogous procedure to that described in the fifth paragraph of the portion of Note [1] immediately above that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (0.2 g) was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline (0.03 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.2 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 5H), 2.6-2.8 (m, 2H), 3.92 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

The N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine used as a starting material was prepared by the reaction of 4-toluenesulphonyl chloride with N-tert-butoxycarbonyl-4-(2-hydroxyethyl)piperidine (International Patent Application WO 00/47212, in example 126 thereof) using an analogous procedure to that described in the third paragraph of the portion of Example 1 that is concerned with the preparation of starting materials.

[4] 7-[3-(4-tert-Butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product gave the following

characterising data: NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.3-3.5 (m, 10H), 3.88 (s, 3H), 4.02 (s, 3H), 4.35 (m, 2H), 7.42 (s, 1H), 7.45 (s, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 492 and 494.

The 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-(3-bromopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 00/47212, example 67; 4.5 g), tert-butyl piperazine-1-carboxylate (2.16 g), sodium iodide (0.079 g), potassium carbonate (2.9 g) and acetonitrile (150 ml) was stirred and heated to reflux for 8 hours. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (5.2 g); NMR Spectrum: ($DMSOd_6$) 1.9 (s, 9H), 1.4 (s, 9H), 1.95 (m, 2H), 2.32 (m, 4H), 2.45 (m, 2H), 3.3 (m, 4H), 3.9 (s, 3H), 4.2 (m, 2H), 5.9 (s, 2H), 7.18 (s, 1H), 7.5 (s, 1H), 8.35 (s, 1H); Mass Spectrum: $M+H^+$ 533.

A mixture of the material so obtained and a saturated methanolic ammonia solution (160 ml) was stirred at ambient temperature for 1.5 days. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (3.6 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 1.98 (m, 2H), 2.3 (m, 4H), 2.45 (m, 2H), 3.25-3.35 (m, 4H), 3.88 (s, 3H), 4.15 (m, 2H), 7.1 (s, 1H), 7.45 (s, 1H), 7.98 (s, 1H); Mass Spectrum: $M+H^+$ 419.

A mixture of the material so obtained, carbon tetrachloride (2.4 ml), triphenylphosphine (4.39 g) and 1,2-dichloroethane (160 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline (3.33 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 2.0 (m, 2H), 2.35 (m, 4H), 2.48 (m, 2H), 3.35 (m, 4H), 4.02 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

[5] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.8 (m, 2H), 3.9 (s, 3H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.45 (s, 1H), 7.46 (s, 1H), 7.8 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 493 and 495.

The 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum and the resultant residue was triturated under diethyl ether. There was thus obtained 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: ($CDCl_3$) 4.09 (s, 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water was decanted and the residual solid was suspended in acetone. After stirring, the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (26.61 g); NMR Spectrum: ($DMSOd_6$) 3.97 (s, 3H), 7.22 (s, 1H), 7.3 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: ($DMSOd_6$) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39 g);

NMR Spectrum: ($CDCl_3$) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows :-

A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate was evaporated under vacuum. The resultant oil was decanted from the additional solid which was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: ($DMSOd_6$) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

[6] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 551 and 553.

The 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

2,3-Epoxypropyl bromide (16.8 ml) was added to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 00/47212, within example 12 thereof; 40 g), potassium carbonate (36 g) and DMF (400 ml) and the resultant mixture was heated to 70°C for 1.5 hours. The mixture was poured into an ice/water mixture (1.5 L) and the precipitate was collected, washed with water (1.6 L) and with diethyl ether (500 ml) and dried under vacuum. There was thus obtained 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (46.7 g) which was used without further purification.

A portion (8 g) of the material so obtained was dissolved in chloroform (120 ml) and morpholine (5.8 ml) was added. The reaction mixture was heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (8.2 g); NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H), 2.5 (m, 2H), 2.6 (m, 2H), 2.7 (m, 2H), 3.5 (br s, 1H), 3.75 (m, 4H), 3.95 (s, 3H), 4.15 (m, 2H), 4.25 (m, 1H), 5.95 (s, 2H), 7.15 (s, 1H), 7.65 (s, 1H), 8.2 (s, 1H).

A mixture of the material so obtained and a saturated methanolic ammonia solution (50 ml) was stirred at ambient temperature for 24 hours. The mixture was evaporated and the

resultant solid was washed with diethyl ether. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (6.34 g); NMR Spectrum: ($DMSOd_6$) 2.4 (m, 6H), 3.55 (m, 4H), 3.85 (s, 3H), 4.0 (m, 2H), 4.15 (m, 1H), 4.95 (br s, 1H), 7.15 (s, 1H), 7.45 (s, 1H), 7.95 (s, 1H).

A mixture of a portion (5.2 g) of the material so obtained, pyridine (1 ml) and acetic anhydride (20 ml) was stirred at ambient temperature for 30 minutes. The mixture was poured into a stirred ice/water mixture and the resultant mixture was stirred for 30 minutes. The mixture was cooled in an ice bath and a saturated aqueous sodium bicarbonate solution was slowly added to adjust the pH to 9. The mixture was extracted with methylene chloride and the organic extract was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (5 g); NMR Spectrum: ($DMSOd_6$) 2.05 (s, 3H), 2.4 (m, 4H), 2.6 (m, 2H), 3.55 (m, 4H), 3.85 (s, 3H), 4.35 (m, 2H), 5.25 (m, 1H), 7.2 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 378.

A mixture of the material so obtained, thionyl chloride (60 ml) and DMF (0.5 ml) was heated to reflux for 1 hour. The mixture was evaporated, toluene was added and the mixture was again evaporated. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic solution was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline (4.12 g); NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.55 (m, 4H), 2.7 (d, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.45 (m, 1H), 7.4 (d, 2H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 396 and 398.

[7] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 537 and 539.

The 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and N-isopropyl-N-methylamine using an analogous sequence of reactions as those described in Note [6]

immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$) 1.0 (d, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.35 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H).

[8] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 549 and 551.

The 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and piperidine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 1.6 (m, 2H), 1.9 (m, 4H), 2.1 (s, 3H), 3.2 (br s, 4H), 3.5 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 5.7 (m, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

[9] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 535 and 537.

The 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and pyrrolidine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.05 (s, 4H), 2.15 (s, 3H), 3.45 (br s, 4H), 3.65 (m, 2H), 4.05 (s, 3H), 4.4 (d, 2H), 5.65 (m, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

[10] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 589 and 591.

The 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-

6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and 1-cyanomethylpiperazine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.65 (br s, 10H), 3.5 (s, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 5.45 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 434 and 436.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSOd_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

Example 3 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-hydroxy-3-piperidinopropoxy)quinazoline dihydrochloride salt

A mixture of 7-(2-acetoxy-3-piperidinopropoxy)-4-(2,4-dichloro-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride (0.062 g) and a saturated methanolic ammonia solution (3 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica (Isolute sorbent from International Sorbent Technology Ltd., ref 9470-0100) using a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in methylene chloride (3 ml) and a 6M solution of hydrogen chloride in isopropanol (0.3ml) was added. Diethyl ether (10 ml) was added and the precipitate was collected, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.054 g); NMR Spectrum: ($DMSOd_6$

and CF_3CO_2D) 1.35-1.52 (m, 1H), 1.55-1.77 (m, 2H), 1.78-1.93 (m, 3H), 2.93-3.12 (m, 2H), 3.20-3.38 (m, 2H), 3.47-3.63 (m, 2H), 3.89 (s, 3H), 4.03 (s, 3H), 4.25 (d, 2H), 4.45-4.56 (m, 1H), 7.45 (s, 1H), 7.48 (s, 1H), 8.20 (s, 1H), 8.88 (s, 1H).

Example 4 4-(2,4-dichloro-5-methoxyanilino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline dihydrochloride salt

Using an analogous procedure to that described in Example 3, 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(2,4-dichloro-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride was reacted with a saturated methanolic ammonia solution to give the title compound; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.22-1.35 (m, 6H), 2.80 (s, 3H), 3.05-3.48 (m, 2H), 3.65-3.73 (m, 1H), 3.89 (s, 3H), 4.03 (s, 3H), 4.22-4.3 (m, 2H), 4.39-4.49 (m, 1H), 7.44 (s, 1H), 7.47 (s, 1H), 7.85 (s, 1H), 8.21 (s, 1H), 8.87 (s, 1H).

Example 5

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c)	Tablet III		mg/tablet
	Compound X		1.0
	Lactose Ph.Eur		93.25
	Croscarmellose sodium		4.0
	Maize starch paste (5% w/v paste)		0.75
	Magnesium stearate		1.0
(d)	Capsule		mg/capsule
	Compound X		10
	Lactose Ph.Eur		488.5
	Magnesium		1.5
(e)	Injection I		(50 mg/ml)
	Compound X		5.0% w/v
	1M Sodium hydroxide solution		15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)		
	Polyethylene glycol 400		4.5% w/v
	Water for injection to 100%		
(f)	Injection II		(10 mg/ml)
	Compound X		1.0% w/v
	Sodium phosphate BP		3.6% w/v
	0.1M Sodium hydroxide solution		15.0% v/v
	Water for injection to 100%		
(g)	Injection III	(1mg/ml, buffered to pH6)	
	Compound X		0.1% w/v
	Sodium phosphate BP		2.26% w/v
	Citric acid		0.38% w/v
	Polyethylene glycol 400		3.5% w/v
	Water for injection to 100%		

(h)	Aerosol I	mg/ml
	Compound X	10.0
	Sorbitan trioleate	13.5
	Trichlorofluoromethane	910.0
	Dichlorodifluoromethane	490.0

(i)	Aerosol II	mg/ml
	Compound X	0.2
	Sorbitan trioleate	0.27
	Trichlorofluoromethane	70.0
	Dichlorodifluoromethane	280.0
	Dichlorotetrafluoroethane	1094.0

(j)	Aerosol III	mg/ml
	Compound X	2.5
	Sorbitan trioleate	3.38
	Trichlorofluoromethane	67.5
	Dichlorodifluoromethane	1086.0
	Dichlorotetrafluoroethane	191.6

(k)	Aerosol IV	mg/ml
	Compound X	2.5
	Soya lecithin	2.7
	Trichlorofluoromethane	67.5
	Dichlorodifluoromethane	1086.0
	Dichlorotetrafluoroethane	191.6

(l)	Ointment	ml
	Compound X	40 mg
	Ethanol	300 µl
	Water	300 µl
	1-Dodecylazacycloheptan-2-one	50 µl

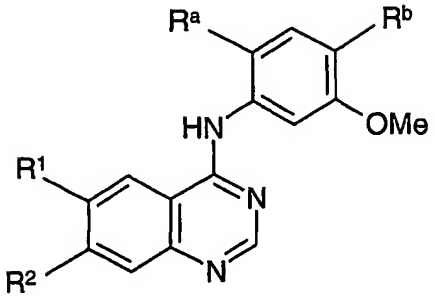
Propylene glycol..... to 1 ml

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

CLAIMS

1. A quinazoline derivative of the Formula I



I

wherein :-

$\mathbf{R^a}$ is chloro, bromo or iodo;

$\mathbf{R^b}$ is chloro, bromo or iodo;

$\mathbf{R^1}$ is hydrogen or (1-6C)alkoxy and $\mathbf{R^2}$ is a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or $\mathbf{R^2}$ is a group of the formula :

$$\text{-}X^2\text{-}R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl, di-[(1-6C)alkyl]amino-(3-6C)alkyl, (2-6C)alkanoylamino-(3-6C)alkyl or (1-6C)alkoxycarbonylamino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^2 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, CH=CH and C≡C wherein R^7 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^7)$, R^7 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl,

(1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^8)$, CO, $CH(OR^8)$, $CON(R^8)$, $N(R^8)CO$, $SO_2N(R^8)$, $N(R^8)SO_2$, $C(R^8)_2O$, $C(R^8)_2S$ and $N(R^8)C(R^8)_2$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same

or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo or thioxo substituents;

or wherein **R^2** is hydrogen or (1-6C)alkoxy and **R^1** is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is heterocyclyl, heterocyclyl-(1-6C)alkyl or heterocyclyloxy-(1-6C)alkyl,

or **R^1** is a group of the formula :

$$-X^2-R^5$$

wherein X^2 is selected from O and $N(R^6)$, wherein R^6 is hydrogen or (1-6C)alkyl, and R^5 is hydroxy-(3-6C)alkyl, (1-6C)alkoxy-(3-6C)alkyl, amino-(3-6C)alkyl, (1-6C)alkylamino-(3-6C)alkyl, di-[(1-6C)alkyl]amino-(3-6C)alkyl, (2-6C)alkanoylamino-(3-6C)alkyl or (1-6C)alkoxycarbonylamino-(3-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, CH=CH and C≡C wherein R^7 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^7)$, R^7 may also be (2-6C)alkanoyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-Q^2$$

wherein X^4 is a direct bond or is selected from O, S, SO, SO_2, $N(R^8)$, CO, $CH(OR^8)$, $CON(R^8)$, $N(R^8)CO$, $SO_2N(R^8)$, $N(R^8)SO_2$, $C(R^8)_2O$, $C(R^8)_2S$ and $N(R^8)C(R^8)_2$, wherein R^8 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^5-R^9$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and R^9 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^6-Q^3$$

wherein X^6 is a direct bond or is selected from O, CO and $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative of the Formula I according to claim 1 wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

or R^2 is a group selected from 3-aminopropoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy or 3-(N-isopropyl-N-methylamino)propoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any pyridyl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

3. A quinazoline derivative of the Formula I according to claim 1 wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 2-imidazol-1-ylethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 4-pyridylmethoxy, 2-pyrid-4-yloxyethoxy, 3-pyrid-2-yloxypropoxy, 3-pyrid-4-yloxypropoxy, 3-azetidin-1-yl-2-hydroxypropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy,

3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy, 2-hydroxy-3-piperazin-1-ylpropoxy, 3-homopiperazin-1-ylpropoxy or 2-hydroxy-3-homopiperazin-1-ylpropoxy,

or R^2 is a group selected from 3-methylaminopropoxy, 2-hydroxy-3-methylaminopropoxy, 3-ethylaminopropoxy, 3-ethylamino-2-hydroxypropoxy, 3-isopropylaminopropoxy, 2-hydroxy-3-isopropylaminopropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(N-ethyl-N-isopropylamino)propoxy, 3-(N-ethyl-N-isopropylamino)-2-hydroxypropoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)-2-hydroxypropoxy, 3-(N-isopropyl-N-methylamino)propoxy or 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any heteroaryl or heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, cyclopropyl, allyl, methoxy and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

4. A quinazoline derivative of the Formula I according to claim 1 wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy,

piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy or 2-hydroxy-3-piperazin-1-ylpropoxy,

or R^2 is a group selected from 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(N-ethyl-N-isopropylamino)propoxy, 3-(N-ethyl-N-isopropylamino)-2-hydroxypropoxy, 3-(N-ethyl-N-methylamino)propoxy, 3-(N-ethyl-N-methylamino)-2-hydroxypropoxy, 3-(N-isopropyl-N-methylamino)propoxy or 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, cyano, amino, vinyl, ethynyl, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, cyclopropyl, allyl, methoxy and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

5. A quinazoline derivative of the Formula I according to claim 1 wherein :

$\mathbf{R^1}$ is methoxy and $\mathbf{R^2}$ is 3-pyrrolidin-1-ylpropoxy, 2-hydroxy-3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 2-hydroxy-3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-hydroxy-3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, 2-hydroxy-3-piperidinopropoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 3-homopiperidin-1-ylpropoxy 3-homopiperidin-1-yl-2-hydroxypropoxy, 3-piperazin-1-ylpropoxy or 2-hydroxy-3-piperazin-1-ylpropoxy,

or R^2 is 3-(N-isopropyl-N-methylamino)-2-hydroxypropoxy,

and wherein any CH_2 or CH_3 group within a R^2 substituent optionally bears a hydroxy group on each said CH_2 or CH_3 group,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl and acetyl,

and wherein any heterocyclyl group within a substituent on R^2 optionally bears 1 or 2 oxo substituents;

$\mathbf{R^a}$ is chloro; and

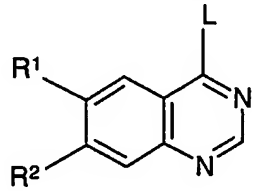
$\mathbf{R^b}$ is chloro;

or a pharmaceutically-acceptable acid-addition salt thereof.

6. A quinazoline derivative of the Formula I according to claim 1 selected from : 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline, 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline, 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline and 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline; or a pharmaceutically-acceptable acid-addition salt thereof.

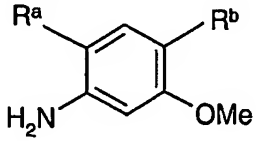
7. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

(a) the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and R^1 and R^2 have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an aniline of the Formula III



III

wherein R^a and R^b have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

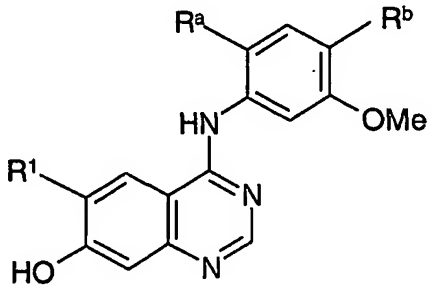
(b) for the production of those compounds of the Formula I wherein R^2 is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is an oxygen atom, the coupling of an alcohol of the Formula

$$Q^1\text{-}OH$$

wherein Q^1 has any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a quinazoline of the Formula V



V

wherein R^1, R^a and R^b have any of the meanings defined in claim 1except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

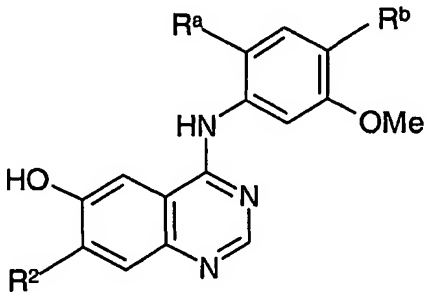
(c) for the production of those compounds of the Formula I wherein R^1 is a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is an oxygen atom, the coupling of an alcohol of the Formula

$$Q^1\text{-}OH$$

wherein Q^1 has any of the meanings defined in claim 1except that any functional group is protected if necessary, with a quinazoline of the Formula VII



VII

wherein R^2, R^a and R^b have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

(d) for the production of those compounds of the Formula I wherein R^1 or R^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein R^1 or R^2 contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine;

(e) for the production of those compounds of the Formula I wherein R^1 or R^2 contains an amino-acyloxy-disubstituted (1-6C)alkoxy group, the acylation of a compound of the Formula I wherein R^1 or R^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group; or

(f) for the production of those compounds of the Formula I wherein an R^1 or R^2 group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R^1 or R^2 group contains a protected hydroxy group;

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, it may be obtained using a conventional procedure.

8. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

9. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 for use in a method of treatment of the human or animal body by therapy.

10. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

INTERNATIONAL SEARCH REPORT

Interna·· · \pplication No
PCT/GB 02/02124

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/94

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 962 458 A (LOHMANN JEAN-JACQUES MARCEL ET AL) 5 October 1999 (1999-10-05) claim 1 (formula I) column 7 (last 2 compounds) column 8 (last compound)	1-10
X	HENNEQUIN L F ET AL: "Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, 1999, pages 5369-5389, XP002164236 ISSN: 0022-2623 table 4 (compounds 10 and 13)	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2002	08/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 35146 A (COCKERILL GEORGE STUART ;GUNTRIP STEPHEN BARRY (GB); GLAXO GROUP L) 15 July 1999 (1999-07-15) claim 1 ---	1-10
A	WO 99 06378 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 11 February 1999 (1999-02-11) claim 1 -----	

INTERNATIONAL SEARCH REPORT

Inte[illegible]nal application No.
PCT/GB 02/02124

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/02124

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